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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/919,143	07/31/2001	Leandro Christmann	AVI 008	2824

26739 7590 07/07/2004

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EXAMINER	
WILSON, MICHAEL C	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 07/07/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/919,143	CHRISTMANN, LEANDRO	
	Examiner	Art Unit	
	Michael C. Wilson	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *19-50* is/are pending in the application.

4a) Of the above claim(s) *19,20 and 22-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 36-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4-12-04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-18 have been canceled. Claims 19-50 have been added.

Election/Restrictions

Newly submitted claims 19, 20 and 22-35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: delivering DNA to an avian embryo has a separate utility: for delivering marker genes to monitor cells during embryonic development. See the restriction requirement sent 10-7-02

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 19, 20 and 22-35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claim Rejections - 35 USC § 112

Claims 21 and 36-50 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

While applicants state no new matter has been added, support for the new claims has not been provided and cannot be found. Support for each phrase,

specifically "providing a microinjection assembly comprising a microscope and a microinjection system" and "positioning the micropipette relative to the avian embryo by monitoring the position of the micropipette" in claim 36, should be provided by page and line number along with explanations if the language is not explicit in the text of the specification. The limitations in dependent claims 37-50 should be pointed out specifically by page and line number or to originally filed claims.

Claims 21 and 36-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed toward delivering nucleic acid into an avian embryo and obtaining a chick. The claims encompass making transgenic avians and cloning avians. When making transgenics, the only enabled purpose for the method is to obtain a germline chimeric chick, i.e. a chick that carries the exogenous nucleic acid in its germ cells and passes the nucleic acid on to its offspring. When cloning, the only enabled purpose for the claimed method is to obtain a viable offspring that has the donor nucleus. Merely transferring exogenous nucleic acids into a recipient embryo does not have an enabled use without obtaining a germline chimera or a clone. The specification teaches the avians produced by the method claimed would be used as protein bioreactors (pg 3, line 11).

The specification summarizes methods of obtaining transgenic mice (pg 2-3) known in the art at the time of filing. However, methods of making transgenic mice do not correlate to making transgenic avians (Proudman of record, 2001, "The quest for transgenic poultry: birds are not mice with feathers" Biotechnology in Animal Husbandry, Vol. 5, Kluwer Academic Publishers, pg 283-299). Proudman summarizes methods of making transgenic mice on pg 284 and concluded, "this technology can only be applied in the mouse." Proudman states "[t]he use of similar techniques to produce transgenic poultry is hampered by major biological differences in the structure and development of mammalian and avian eggs" (pg 284, 2nd full ¶).

More specifically, the specification summarizes methods of making transgenic avians by introducing exogenous DNA into avian eggs known in the art (pg 3-5). Proudman also reviews the progress achieved in the field of making transgenic poultry, and states, "[t]he technique of microinjection that has proven successful in other species is not directly applicable to avian species" (pg 284, last sentence). That is because of the difference between the mammalian and avian early embryo (pg 285, first two ¶). The specification does not teach how to obtain germline chimeras using microinjection. The specification does not correlate methods known in the art capable of producing germline chimeras to the method of microinjection described in the specification such that one of skill could produce a germline chimeric chick. Without such guidance, it would require one of skill undue experimentation to make a germline chimeric avian using microinjection as described in the specification. Therefore, the specification does

not overcome the unpredictability in the art by teaching how to obtain a germline chimeric chick by microinjection.

The specification describes methods of transferring exogenous nucleic acids into chickens but does not teach transferring exogenous nucleic acids into other types of birds (claim 13). The specification does not correlate the structure of chicken embryos to any other bird embryos. Without such guidance it would require one of skill undue experimentation to use microinjection to make any avians as broadly claimed. Therefore, the claims should be limited to chickens.

Claim 48 requires delivering a nucleic acid in the form of spermatozoon or an isolated cell nucleus (claim 48). Claims 43-46 require using the microinjection assembly has an oscillator, specifically a piezo-electric oscillator, which was only used in the art for delivering sperm or an isolated cell nucleus (Dozortsev, Zygote, May 1998, Vol. 6, No. 2, pg 143-147, and Korfiatis, Cloning and Stem cells, 2001, Vol. 3, No. 3, pg 125-138, for example). The specification contemplates removing the nucleus of an avian egg (pg 37, Example 3) and transplanting a donor nucleus into the egg (pg 39, Examples 5 and 6), i.e. cloning. The art at the time of filing did not teach how to clone avians. Therefore, it was unpredictable how to clone avians at the time of filing. The specification does not teach obtaining a viable offspring. The specification does not adequately correlate methods known in the art capable of cloning to the method of microinjection described in the specification. The specification does not correlate the structure of mammalian embryos capable of cloning known in the art to avians embryos such that one of skill could use mammalian cloning methods to clone avians. Without

such guidance it would require one of skill undue experimentation to use microinjection to make avians that carry the donor nucleus. Therefore, claims 43-46 and 48, related to cloning or nuclear transfer, are not enabled because the specification does not overcome the unpredictability in the art by providing adequate guidance for one of skill to clone an avian.

Applicants argue the invention is based on the microinjection system, which has the "capability to visualize the micropipette relative to the embryo" (pg 5 of response, last sentence of 5th full ¶). Microinjection systems in the art have a needle positioned "in front of the injection site in which case the operator cannot visualize whether the micropipette is in the germinal disk or know the depth of the micropipette within the ooplasm." Applicants provide Figure A.

Figure A cannot be seen because it is completely black with a faint appearance of a grid. No micropipette tip or embryo can be seen, and the angle at which the embryo is injected and monitored cannot be determined. Therefore, arguments relating to Figure A are moot.

The meaning of applicants' other arguments cannot be determined. Applicants appear to be saying the angle at which the needle approaches the embryo relative to the angle at which the embryo is visualized from the microscope is the basis of the invention. However, it cannot be determined how one visualizes the micropipette "relative" to the embryo or what applicants consider the "front" of the injection site as argued. Applicants argue the invention is better than those known in the art, such as those used by Love or Naito. Applicants' argument is not persuasive. It is not readily

apparent that Love or Naito used a microinjection system that prevented them from visualizing the depth of the micropipette or that the microinjection system used by Love or Naito was more disruptive to the embryo than applicants' microinjection system. In addition, visualizing the embryo differently than Love or Naito is inadequate to overcome the unpredictability in the art of making transgenic avians. Finally, it is not clear that applicants have limited the claims to an angle of the needle as it approaches the embryo and the angle at which the embryo is visualized from the microscope that reflects applicants' invention (see 112/2nd). In conclusion, applicants have not taught how to overcome the major biological differences in the structure and development of mammalian and avian eggs (the unpredictability in the art) such that transgenic avians could be made. The specification does not correlate methods known in the art capable of producing germline chimeras to the method of microinjection described in the specification such that one of skill could produce a germline chimeric avian. Without such guidance, it would require one of skill undue experimentation to make a germline chimeric avian using microinjection as described in the specification. Therefore, the specification does not making transgenic avians as claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 21 and 36-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The distinction between a "microinjection assembly" and a "microinjection system" in claim 36 cannot be determined. It is unclear if the metes and bounds of a "microinjection assembly" is the same as a "microinjection system" or broader than a "microinjection system."

The step of "positioning" in claim 36 is wholly unclear. It is unclear how a micropipette is positioned relative to an embryo by "monitoring the position of the micropipette." It is unclear if "monitoring" is part of the "positioning" step or if it is a second step. The "position" of the micropipette relative to the embryo is never set forth. The "position" from which the micropipette is "monitored" relative to the embryo or needle is never set forth. The phrase ""monitoring the position of the micropipette from an angle that is other than parallel to a line between a tip of the micropipette and the avian embryo" is unclear. The metes and bounds of the numerous lines between a micropipette tip and an embryo cannot be determined because an embryo is irregular in shape with an irregular surface and is bigger than the micropipette tip. Therefore, the angles that are not parallel to those lines as claimed cannot be determined. In fact, it appears that the angle of "monitoring" encompasses angles that would not result in visualizing the position of the micropipette or embryo.

It is unclear why the nucleic acid is "delivered" to an embryo when an "injection" system is being used. The step should be limited to "injecting the nucleic acid into the avian embryo."

There should be an "and" after "to a recipient avian female;".

The period after "develop into a chick" should be a comma.

Merely allowing a chick to develop from an embryo that had a nucleic acid delivered does not necessarily produce a transgenic avian as claimed. For a chick to be a transgenic it must incorporate the nucleic acid into its genome and express the protein encoded by the nucleic acid. The phrase "thereby producing a transgenic avian" is not a clear, positive step indicating that such an avian has been made.

The phrase "the positioning the micropipette" does not make sense in claims 40 and 41.

The metes and bounds of what applicants consider an "oblique macro-monitoring system" in claim 40 cannot be determined. How big is the monitoring system? To what does "oblique" refer?

The metes and bounds of what applicants consider applying "an oscillation" to the microinjection system cannot be determined. It is unclear if shaking the table is encompassed by the claim or if the claim is limited to some mechanical oscillation.

The limitation in claim 48 is backwards. The limitation is further limiting the nucleic acid in claim 36, so the limitation should begin "wherein the nucleic acid is..." and not begin with the nucleus or sperm. As written, the species comprise the genus, which cannot be.

The limitation in claim 49, "is an embryo of a [sic] of an avian" is grammatically incorrect. Here also, the limitation can be more clearly set forth by stating, "wherein the avian embryo is a chicken, turkey, quail... ...or swan embryo."

The metes and bounds of what applicants consider "fistulation" in claim 50 cannot be determined.

The distinction between "fistulation" and "surgically exposed avian infundibulum" cannot be determined in claim 50. Use of the phrase "or by delivering to a" is redundant. Deleting "by fistulation" would cause the limitation to read "wherein the avian embryo is delivered to the recipient avian female by delivering to a surgically exposed avian infundibulum." The phrase does not clearly set forth that the avian embryo is delivered into a recipient avian infundibulum, that the embryo is delivered by a surgical procedure or that exposing the infundibulum of an avian by surgery is a clear, positive step in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 21, 36-42 and 47-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tanaka (1994, J. Reprod. Fert., Vol. 100, pg 447-449) in view of Sang (Molecular Reproduction and Development, 1989, Vol. 1, pg 98-106).

Tanaka (1994, J. Reprod. Fert., Vol. 100, pg 447-449) taught delivering the zygote into the birth canal of a hen and allowing the zygote to become a chick (pg 447, col. 2, "Materials and Methods;" pg 448, Fig. 1; pg 448, col. 1, line 4; pg 448, col. 2, 1st full ¶, line 9). Tanaka taught delivering DNA to the zygote before delivering the zygote to the recipient hen (pg 449, col. 1, last ¶). Tanaka did not teach delivering the DNA to the zygote with a microinjection assembly comprising a microscope and a microinjection system having a micropipette as claimed.

However, Sang (Molecular Reproduction and Development, 1989, Vol. 1, pg 98-106) taught delivering DNA to a chicken zygote and allowing the zygote to become a chick (pg 99, col. 1).

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to deliver DNA to a zygote, deliver the zygote into the birth canal of a hen and allow the zygote to become a chick as taught by Tanaka wherein the DNA was delivered using the micromanipulator taught by Sang. One of ordinary skill in the art at the time the invention was made would have been motivated to deliver the DNA of Tanaka using the micromanipulator taught by Sang because Sang had increased survival rate as compared to Tanaka (pg 100, lines 1-2, of Sang as compared to the last ¶ of Tanaka).

The microinjection system taught by Sang has a micromanipulator and a micropipette and must inherently comprises a microscope as claimed because micromanipulator was inherently attached to a microscope (see definitions of "micromanipulator" by Dorlands Medical Dictionary and by Drug Discovery and Development). For Sang to have determined the DNA was inserted at a depth of 140-200 μm beneath the vitelline membrane (pg 99, col. 1, 2nd full ¶, 1st sentence), the embryo must have been monitored by a microscope as claimed, and the microinjection system taught by Sang inherently comprised a microscope as claimed.

A zygote is an embryo because it is an organism in the early stages of development (see definition of "embryo" by Stedman's Medical Dictionary). In addition, a zygote is an embryo because Tanaka, one of ordinary skill in the art at the time the invention was made, referred to the one-cell fertilized ovum as an embryo (last ¶).

The limitation of "positioning the micropipette relative to the embryo by monitoring the position of the micropipette from an angel that is other than parallel" has been included because the phrase is so unclear (see 112/2nd). In addition, the angle of the pipette would have been visible from the side of the microscope, which appears to meet the limitation because the pipette is being visualized from an angle that is not parallel to the line between the tip of the micropipette and the embryo.

Thus, Applicants' claimed invention as a whole is *prima facie* obvious in the absence of evidence to the contrary.

Double Patenting

Claim 36 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 21. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Wilson who can normally be reached at the office on Monday, Tuesday, Thursday and Friday from 9:30 am to 6:00 pm at 571-272-0738.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Amy Nelson, can be reached on 571-272-0804.

The official fax number for this Group is (703) 872-9306.

Michael C. Wilson

MICHAEL WILSON
PRIMARY EXAMINER